II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-60 were pending in the case at the time of the Action. Claims 31, 52, and 53 have been amended. Support for the amendments to the claims can be found generally throughout the specification, such as in the claims as originally filed. Claims 30 and 34-37 have been canceled without prejudice or disclaimer. No new claims have been added. Therefore, claims 1-60 are presently under consideration.

B. Information Disclosure Statement

According to the Action, the citations on the PTO-1449 of documents C1, C2, C23, C24, and C95 are said to not fully comply with the requirements of 37 CFR 1.98(b)(c), which provides that non-patent documents be identified by date of publication, location of publication, *etc.* Applicants have concurrently filed with this response revised PTO-1449 documents that include the required information.

C. The Rejections Under 35 U.S.C. §102 are Overcome

1. Rejections Based on Clayman As Evidenced By Oda *et al.* and Flaitz *et al.*

Claims 1-12, 15, 18, 23-28, 30, 33, 36, 38-48, 51, and 54 have been rejected under 35 U.S.C. §102(a) as being anticipated by Clayman (C95 in IDS filed 8/16/04) as evidenced by Oda *et al.* and Flaitz *et al.*, and as evidenced by the Recombinant DNA Advisory Committee (RAC), Minutes of Meeting March 8, 2001 (hereinafter "RAC").

Clayman is said to describe a clinical protocol for treating humans with premalignancies of squamous epithelium in the oral cavity with an adenoviral vector encoding p53 under the control of the CMV promoter by intramucosal injection in the area of the lesion followed by topical application of a mouthwash comprising the vector. The Examiner admits that Clayman

does not mention papilloma virus infection of cells in the lesion. The Examiner argues that this characteristic is inherent in a substantial fraction of patients that would be the target of the disclosed treatment because Oda discloses that up to 90% of oral cancers have been reporter to contain HPV DNA and Flaitz discloses that about 50% of oral epithelial dysplasias are infected with HPV, and between one-third to one-half of oral squamous cell carcinoma involve HPV infection. Applicants respectfully traverse.

a) No Inherent Anticipation of Claims 1-12, 15, 18, 23-28, 38-48, 51, and 54

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

Clayman does not anticipate because it neither expressly or inherently describes the claimed invention. As admitted by the Examiner, Clayman does not mention papilloma virus infection. Therefore, Clayman does not expressly anticipate.

Nor is there inherent anticipation. Inherent anticipation arises when "the prior art necessarily functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co.*, 190 F.3d at 1347. (citing *In re King*, 801 F.2d 1324, 11326 (Fed. Cir., 1986); see also *Atlas Powder Co.,* 190 F.3d at 1347-48). It is well-established that:

> "inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."

MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981).

In *MEHL/Biophile*, Milgraum contended that all of the claims of MEHL/Biophile's patent directed to a method for removing hair using a laser were anticipated by an instruction

manual. *See MEHL/Biophile,* 192 F.3d 1362. The claims included the step of "aligning a laser light applicator substantially vertically over a hair follicle opening." *Id.* The manual taught aiming the laser at skin pigmented with tattoo ink. Milgraum contended that the claims were inherently anticipated because an operator of the laser could use the laser according to the manual without necessarily aligning the laser substantially vertically over a hair follicle opening. *Id.* The Court held that "the possibility of such an alignment does not legally suffice to show anticipation" and that "[o]ccasional results are not inherent." *MEHL/Biophile,* 192 F.3d at1365.

In the instant case, the facts are not dissimilar. A hyperplastic lesion might contain cells containing HPV, or it might not. It does not necessarily include such cells. The mere fact that a cell of a hyperplastic lesion might occasionally contain HPV DNA is not sufficient to establish inherent anticipation. As noted in MEHL/Biophile, ***occasional results are not inherent.*** Without an inherent teaching regarding HPV-transformed cells, there can be no anticipation.

b) Claims 30 and 36

As set forth in the Amendment, claims 30 and 36 have been canceled without prejudice or disclaimer. Applicants, in canceling these claim, in no way concede that these claim are anticipated by Clayman or any of the other references set forth in the Action. Further, Applicants reserve the right to prosecute this claim in any application that claims priority to the instant application.

c) Claim 33

Claim 33 includes the limitation "a liquid carrier formulated for vaginal delivery." A douche is a jet of liquid applied to a body part or body cavity. In the context of claim 33, which includes the limitation "a liquid carrier formulated for vaginal delivery," a douche is a jet of liquid applied to the vagina. Clayman fails to anticipate claim 33 because it does not expressly or inherently disclose any douche solution formulated for vaginal delivery. There is no

indication in Clayman that the formulations set forth in Clayman are suitable for vaginal delivery. Clayman makes absolutely no mention of vaginal delivery. Rather, it is directed to treatment of disease of the oral cavity. Furthermore, there is no disclosure in Clayman pertaining to any ***jet of liquid*** applied to any part of the body, vagina or otherwise. Therefore, Clayman fails to anticipate claim 33.

d) Comment

In the first paragraph addressing this rejection, the Examiner indicates that the rejection is "as evidenced by Recombinant DNA Advisory Committee (RAC), Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services." Page 3, paragraph 2. However, there is no further mention of this reference in the rejection. Therefore, Applicants have addressed this rejection as if it pertained to Clayman in view of Oda *et al.* and Flaitz *et al.*

On page 4, second paragraph of the Action, it is indicated that "this presentation appears to have been presented to the RAC in a public meeting on 3/8/01." The presentation that is the subject of this sentence appears to be Clayman, as it is discussed in the preceding paragraphs. Applicants note, however, that Clayman was not a presentation to the Recombinant DNA Advisory Committee, but was a presentation at Introgen Therapeutics, Inc., as set forth in the Information Disclosure Statement.

e) Conclusion

In view of the above, it is respectfully submitted that the rejection of claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 should be withdrawn.

2. Rejections Based on RAC Minutes, as evidenced by Oda *et al.* and Flaitz *et al.*

Claims 1-12, 15, 18, 23-28, 30, 33, 36, 38-48, 51, and 54 have been rejected under 35 U.S.C. §102(b) as being anticipated by the RAC as evidenced by Oda *et al.* and Flaitz *et al.* RAC is said to describe a clinical protocol for treating humans with premalignancies of squamous epithelium in the oral cavity with an adenoviral vector encoding p53 under control of the CMV promoter by intramucosal injection in the area of the lesion followed by topical application of a mouthwash comprising the vector. The Examiner, who admits that RAC does not disclose papilloma virus infection in cells in the lesion, argues that this characteristic is inherent in view of Oda *et al.* and Flaitz *et al.*, as discussed above. Consequently, it is argued that one of ordinary skill in the art of oral cancer would have been aware that treatment of hyperplastic lesions as described in RAC would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells. Applicants respectfully traverse.

a) No Inherent Anticipation of Claims 1-12, 15, 18, 23-28, 38-48, 51, and 54

RAC does not anticipate claims 1-12, 15, 18, 23-28, 38-48, 51, or 54 because it neither expressly or inherently describes each limitation of the claimed invention. As admitted by the Examiner, RAC does not disclose papilloma virus infection of cells in the lesion. Thus, RAC does not expressly anticipate.

Nor is there inherent anticipation. As discussed above, inherent anticipation arises when "the prior art necessarily functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co.*, 190 F.3d at 1347. (citing *In re King*, 801 F.2d 1324, 11326 (Fed. Cir., 1986); see also *Atlas Powder Co.,* 190 F.3d at 1347-48). As noted above, "inherency ... may not be established by probabilities or possibilities." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981).

As noted in *MEHL/Biophile*, "[o]ccasional results are not inherent." The mere fact that a cell of a hyperplastic lesion might occasionally contain HPV DNA is not sufficient to establish inherent anticipation. Without an inherent teaching regarding HPV-transformed cells, there can be no anticipation.

b) Claims 30

As discussed above, claim 30 has been canceled without prejudice or disclaimer. Further, Applicants reserve the right to prosecute this claim in any application that claims priority to the instant application.

c) Claim 33

Claim 33 includes the limitation "a liquid carrier formulated for vaginal delivery." A douche is a jet of liquid applied to a body part or body cavity. In the context of claim 33, which includes the limitation "a liquid carrier formulated for vaginal delivery," a douche is a jet of liquid applied to the vagina. RAC fails to anticipate claim 33 because it does not expressly or inherently disclose any douche solution formulated for vaginal delivery. There is no indication in RAC that the formulations set forth in RAC are suitable for vaginal delivery. RAC makes absolutely no mention of vaginal delivery. Rather, it is directed to treatment of disease of the oral cavity. Furthermore, there is no disclosure in RAC pertaining to any jet of liquid applied to any part of the body, vagina or otherwise. Therefore, RAC fails to anticipate claim 33.

d) Claim 36

As set forth above, claim 36 has been canceled without prejudice or disclaimer. Therefore, the rejection of this claim is moot.

e) Conclusion

In view of the above, it is respectfully submitted that the rejection of claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 should be withdrawn.

3. Rejections Based on Nielsen as Evidenced by Oda *et al.* and Flaitz *et al.*

Claims 1-14, 19-29, 34-50, and 55-60 have been rejected under 35 U.S.C. §102(b) as being anticipated by Nielsen *et al.*, U.S. 2001/0044420 ("Nielsen"), as evidenced by Oda *et al.* and Flaitz *et al.* Nielsen is said to describe the treatment of cancer in general, including cervical cancer and head and neck cancer, by a combination of p53 gene therapy and gemcitabine chemotherapy. It is said to disclose non-viral lipid-based plasmid delivery or delivery via a viral vector, such as adenovirus. It is also said to disclose a p53 coding sequence under the control of a constitutive or tumor specific promoter. It is also said to disclose topical delivery, such as to a surgical wound following tumor resection. The Examiner, who admits that Nielsen does not mention papilloma virus infection of cells of the lesions, again relies on Oda *et al.* and Flaitz *et al.* to support an argument based on inherency in the manner discussed above. Applicants respectfully traverse.

a) No Inherent Anticipation of Claims 1-14, 19-29, 38-50, and 55-60

Nielsen does not anticipate because it neither expressly or inherently describes the claimed invention. As admitted by the Examiner, Nielsen does not disclose papilloma virus infection of cells in the lesion. Thus, Nielsen does not expressly anticipate.

The question that remains is whether there is inherent anticipation. As with the previous prior art rejections, there is no inherent anticipation. As discussed above, inherent anticipation arises when "the prior art necessarily functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co.*, 190 F.3d at 1347. (citing *In re King*, 801 F.2d 1324, 11326 (Fed. Cir., 1986); see also *Atlas Powder Co.*, 190 F.3d at 1347-48). As noted above,

> "inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."

MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981).

As noted in *MEHL/Biophile*, "[o]ccasional results are not inherent." The mere fact that there might be a possibility that hyperplastic lesion might contain one or more cells that contain HPV DNA is not sufficient to establish inherent anticipation. As taught by the literature cited by the Examiner, it is quite possible that each of the cells of a hyperplastic lesion might be entirely free of HPV DNA. It is of no consequence whether it is more likely that this is not the case. Because there is a chance that cells of a hyperplastic lesion may be entirely free of HPV DNA, there can be no inherent anticipation.

b) Claims 34-37

Claims 34-37 have been canceled without prejudice or disclaimer in accordance with the Amendment set forth herein. Applicants, by canceling these claims, in no way concede that the claims are anticipated by Nielsen. Applicants reserve the right to further prosecute these claims in an application that claims priority to the present application.

c) Conclusion

In view of the above, claims 1-14, 19-29, 38-50, and 55-60 are not anticipated by Nielsen. Therefore, it is respectfully submitted that the rejection of these claims should be withdrawn.

4. Rejections Based on El-Deiry

Claims 1-15, 18-30, 33-51, and 54-60 have been rejected under 35 U.S.C. §102(b) as being anticipated by El-Deiry *et al.* (WO 99/66946; "El-Deiry"). The invention of El-Deiry is said to relate to gene therapy with a transgene encoding p73, which is said to be a "homolog" of p53. See, *e.g.*, Abstract. According to the Examiner, given the definition of "p53" in the instant

specification, which includes homologues of p53 from other species, p73 is embraced by the term "p53" recited in the instant claims. Applicants respectfully traverse.

In accordance with Applicants' specification, "the term 'p53' is intended to refer to the exemplified p53 molecules as well as all p53 homologues from other species." Specification, page 14, lines 5-6. The Examiner cites El-Deiry as allegedly teaching a homologue of p53. However, the molecule set forth is not a "homologue" of p53 as the term "homologue" is used in Applicants' specification and as the term "homologue" would be understood by one of ordinary skill in the art. In Applicants' specification, "homologue" is a molecule that is the same type, but from a species other than the exemplified species, which is human. Thus, a "homologue" of human p53 is a molecule of the same type but from a different species (*e.g.*, mouse p53, rat p53, etc.).

The molecule that the Examiner cites as teaching a "homologue" of p53 in El-Deiry is not a "homologue" because it is not a p53 molecule from a species other than human. The p73 molecule taught in El-Diery is a molecule that is not of the same type as p53. Further, it is not from a different species because it is a human p73. Even if it were from a species other than a human it would still not be a homologue because it is a molecule that is of a distinct type than p53.

The fact that El-Deiry uses the term "homolog" to refer to p73 is not dispositive. "During patent examination, the pending claims must be given their 'broadest reasonable interpretation consistent with the specification.'" *MPEP* §2111, citing *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The instant specification is consistent with use of the term "homologue" to refer to the same type of molecule in a different species.

El-Deiry indicates that p73 is structurally and functionally dissimilar from p53. In particular, El-Deiry indicates that unlike p53, p73 is not targeted for degradation by E6. Furthermore, p73 is of a different structure than p53. Thus, p73 is both structurally and functionally distinct from p53.

Additionally, Applicants have submitted the Declaration of Louis Zumstein, PhD, under 37 C.F.R. §1.132 as evidence of what a person of ordinary skill in the art would consider a homologue of p53 (Exhibit 1). In accordance with the requirement of 37 C.F.R. §1.132, Applicants have provided in their declaration a showing of evidence of such character and weight as to establish that El-Diery fails to anticipate the claimed invention within the meaning of 35 U.S.C. §102(b).

Dr. Zumstein, a person of skill in the art with over 13 years of experience in the biotechnology field, has indicated that, in his opinion, p73 is not a homologue of p53. He bases this opinion on the fact that while p73 and p53 share some similar functions, there are other characteristics that distinguish these two proteins.

> Furthermore, as a scientist in the biotechnology field, it is my belief that p73 is not a homologue of p53. More specifically, while p73 and p53 do share some similar functions, and share some sequence similarities, there are important characteristics that distinguish the two proteins. For example, in contrast to p53 deficient mice, those mice lacking p73 show no increased susceptibility to spontaneous tumorigenesis. Additionally, p73 is not activated by DNA damage, unlike p53.

Declaration of Luis Zumstein, PhD, ¶ 6.

In addition, Dr. Zumstein indicates that, in his opinion, a reading of page 14, lines 5-10 of the instant specification would indicate to a person of ordinary skill in the art that the term "homologue" would refer to both human and non-human p53, but not to proteins which might share certain functional characteristics, *i.e.* p73.

> As a scientist in the biotechnology field, I feel that the aforementioned lines regarding p53 indicate that this passage is specific for human p53 and p53 in other species. I do not believe from reading this passage that "p53" as used in this passage would refer to proteins other than p53 that might share some functional characteristics with p53,.

Declaration of Luis Zumstein, PhD, ¶ 5.

Therefore, because El-Diery does not disclose treatment of papilloma-virus transformed cells with "p53," it fails to anticipate the claimed invention.

D. The Rejections Under 35 U.S.C. §103(a) are Overcome

Claims 16, 17, 31, 32, 52, and 53 have been rejected under 35 U.S.C. §103(a) as being unpatentable over either RAC, as evidenced by Oda *et al.* and Flaitz *et al.*, as applied to claims 1-12, 15, 18, 23-28, 30, 33, 36, 38-48, 51, and 54 above, or El-Deiry as applied to claims 1-15, 18-30, 33-51, 54-60 above, and further in view of Zhang *et al.* (WO 00/29024; "Zhang"). The teachings of RAC, Oda *et al.*, Flaitz *et al.*, and El-Deiry are as discussed above. Zhang *et al.* is said to generally describe pharmaceutical compositions for gene therapy comprising adenoviral vectors, and use of flavorants in compositions for oral delivery. The Action asserts that it would have been obvious to one of ordinary skill in the art of gene therapy to include a flavorant, in a mouthwash containing a vector. Applicants respectfully traverse.

1. There is No *Prima facie* Case of Obviousness Because the Combination of References Does Not Teach or Suggestion Each Limitation of the Claimed Invention

In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (3) there must be a reasonable expectation of success. *Manual of Patent Examining Procedure* § 2142. See also *In re Vaeck*, 947 F.2d 488, 20

U.S.P.Q. 2d 1438 (Fed Cir. 1991) (emphasizing that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be both found in the prior art, and not based on applicant's disclosure). It is important to note that all three elements must be shown to establish a *prima facie* case of obviousness.

There is no *prima facie* case of obviousness because the Examiner has not set forth that the combination of references teaches or suggests each limitation of the claimed invention. The Examiner argues that RAC and El-Deiry both describe liquid compositions for oral delivery of the vector to HPV-transformed cells. No such teaching or suggestion has been set forth in either reference. Neither RAC nor El-Deiry make mention of a liquid composition for oral delivery of a vector to HPV transformed cells. For the reasons discussed above, the discussion of which is incorporated into this section, RAC and El-Deiry do not address delivery of any vector to an HPV-transformed cell or to any lesion that includes an HPV-transformed cell.

The Examiner has cited Oda *et al.* and Flaitz *et al.* as allegedly teaching that a certain percent of oral dysplastic and oral cancer cells contain HPV DNA. However, he has not cited any teaching or suggestion in either reference pertaining to treatment involving delivery of a vector to an HPV-transformed cell.

Zhang *et al.*, cited as teaching flavorants, is not dispositive. The Examiner has cited no disclosure in Zhang *et al.* pertaining to oral delivery of any vector to an HPV-transformed cell. Applicants invite the Examiner to identify any such teaching or suggestion in this reference. Applicants further point out that none of the references teach the flavorants set forth in claim 17.

2. The Combination of References Does Not Provide Any Motivation to One of Ordinary Skill in the Art to Modify/Combine the Reference Teachings to Lead to the Claimed Invention

Furthermore, the Examiner has not cited any section in any of the cited references that would provide any motivation to one of ordinary skill in the art to lead to the claimed invention. It is the Examiner's responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Intl*, 745 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). Neither RAC nor El-Deiry provide any mention of HPV-transformed cells. Further, the Examiner has cited no section of either Flaitz *et al.* or Oda *et al.* to provide any motivation to treat any HPV-transformed cell with p53. Zhang *et al.*, cited as teaching a flavorant, does not provide the missing motivation to modify/combine reference teachings to lead to the claimed invention.

3. Conclusion

In view of the above, the Examiner has failed to meet his burden of establishing a *prima facie* case of obviousness. Therefore, it is respectfully requested that this rejection should be withdrawn.

E. Request for Information

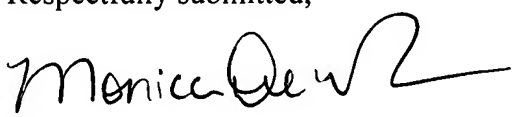
Regarding document C95 cited on the PTO-1449 filed 8/16/04 (Clayman), the Examiner has requested certain information in order to determine whether C95 also qualifies as prior art under 35 U.S.C. §102(b), in light of *In re Klopfenstein*, 72 USPQ2d 1117 (Fed. Cir. 2004). This information includes the date, location, and audience (including their level of expertise), the length of time the information was displayed, medium used to display the information, etc. This information was presented at the March 8, 2001 NIH Recombinant DNA Advisory Committee

Meeting. The presentation format was a Microsoft PowerPoint slide show lasting approximately 15 minutes in length, and was presented at NIH, located in Bethesda, Maryland. The meeting was open to the public, and notice of the meeting was published in the Federal Register as required by NIH guidelines. A webcast of the meeting is available at http://www4.od.nih.gov/oba/rac/meeting.html. Those in attendance may be found in the corresponding minutes file of the same meeting.

F. Conclusion

It is submitted that in light of the foregoing amendments and remarks, the invention embraced by the pending claims as been shown to be patentable, and favorable reconsideration is earnestly solicited. The Examiner is invited to contact the undersigned attorney with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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